

Exhibit 163

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EXPERT REPORT OF MARK A. SCHUMACHER, M.D., Ph.D.

MARCH 25, 2019

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I. INTRODUCTION

1. My name is Mark A. Schumacher, M.D., Ph.D. I have been retained by Plaintiffs Cuyahoga County and Summit County to offer my expert opinions on issues related to the medical use of opioids for the treatment of pain, the conduct of opioid manufacturers relating to the marketing and promotion of prescription opioids, and related topics.

2. My curriculum vitae, a copy of which is attached as **Appendix 1** to this report, describes my education, background, qualifications, and my publications. I have not testified in deposition or at trial in the last four years.

3. I am being compensated at a rate of \$450 per hour for my services in this litigation. I am also being reimbursed for all reasonable expenses incurred for my work on this litigation. No part of my compensation is contingent upon the outcome of this litigation, and I have no interest in the litigation or with either party.

4. This report contains a true and accurate statement of my opinions in this matter. The matters cited in this expert report are based on my personal knowledge, education, and years of medical experience and, if called to testify, I will testify to the same effect. These opinions are based on my education, training and experience as well as the data, evidence, and literature cited herein and are offered to a reasonable degree of medical certainty. I reserve the right to supplement my analysis and opinions based on additional evidence or information that is made available to me after the date of this report, including additional expert disclosures made after March 25, 2019, as approved by the Court.

II. SUMMARY OF OPINIONS:

5. It is my opinion, based on my expertise in the field of pain management, that the increased prescribing of opioids in the United States has caused tremendous harm that would not have occurred if not for the actions of the companies that aggressively promoted the use of

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opioids for a wide array of conditions beyond short-term acute pain, cancer pain from active disease, and end-of-life and hospice care.

6. The prevalence of chronic pain is a valid concern but should not be confused with underutilization of opioids. In addition, to the extent that there was some amount of under-treated pain, it does not follow that the best treatment then (or now) would have been an opioid; indeed, in the vast majority of cases the best treatment would have been something other than an opioid, and likely a combination of physical, pharmacologic, and behavioral approaches.

7. More specifically, I provide the following opinions based on my experience, review of academic literature, and review of documents and certain information produced in discovery in this action:

8. It is my opinion to a reasonable degree of certainty in the field of pain medicine that the medical standard of care for treating both chronic and acute pain was changed as a result of widespread promotion and marketing of opioids by Defendants¹ that trivialized the risk of addiction and exaggerated the benefits of long-term opioid use.

9. It is my opinion to a reasonable degree of certainty in the field of pain medicine that Defendants influenced physicians through direct-to-physician marketing, medical education, and industry-sponsored and -funded Key Opinion Leaders (“KOLs”) to prescribe long-term opioids based on misinformation about the risks and benefits of chronic opioid use.

10. It is my opinion to a reasonable degree of certainty in the field of pain medicine that for the vast majority of chronic pain patients, the risks of prescription opioids significantly

¹ “Defendants” as used herein refers to the Defendant manufacturers of branded and generic opioid products in the actions brought by Plaintiffs Cuyahoga County and Summit County: Purdue Pharma, Endo, Janssen, Teva, Cephalon, Mallinckrodt, Actavis, and Allergan.

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outweigh any benefits, and that at most, a small percentage of chronic pain patients achieve meaningful relief from the long-term use of opioids.

11. It is my opinion to a reasonable degree of certainty in the field of pain medicine that even for those indications for which opioids are effective, such as trauma or post-operative pain, the risks of prescribing opioids are significant such that non-opioid alternatives or multimodal analgesia should be used whenever possible to reduce opioid use.

III. BACKGROUND

A. General qualifications and background

12. I am a Professor and Chief of the Division of Pain Medicine in the Department of Anesthesia and Perioperative Care, University of California, San Francisco (UCSF). My education and training include a PhD (Physiology and Pharmacology) and M.D. at the University of California, San Diego. Following an internal medicine internship at Cedars Sinai Medical Center, I completed a residency in anesthesiology at UCSF and devoted my academic career to advance pain medicine through clinical care, teaching and research. I advanced Clinical Pain care at UCSF through the introduction of low-dose ketamine, a non-opioid analgesic adjunct that decreases opioid tolerance, opioid requirements and reduces hyperalgesia (Anesthesia & Analgesia 2001); introduced multimodal analgesia for orthopedic joint surgery to minimize opioids and enhance early mobilization and discharge; served as Director of UCSF Pain Services 2010-2015 and am currently serving as Chief of Pain Medicine since 2010; and directed three UCSF Pain Summits (2011, 2013, 2015). I also served on the National Academies of Sciences, Engineering, and Medicine, Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse - Consensus Report, July 2017: "Pain Management and the Opioid Epidemic" (R. Bonnie 2017).

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13. As part of my teaching responsibilities, I have instructed medical students (Anesthesia 110) residents and fellows in pain management; served as Director of the NIH Center of Excellence in Pain Education at UCSF; and co-authored a chapter on “Opioid Analgesics & Antagonists” in Katzung’s *Basic and Clinical Pharmacology* 8th – 14th edition. My original research on pain includes, as co-author, isolation and characterization of the Capsaicin Receptor TRPV1 (Caterina et al. 1997), a break-through in identifying a novel pain receptor and non-opioid analgesic target; and more recently, identifying Transcription Factor Sp4 as being required for hyperalgesic persistence (Sheehan et al. 2019), proposed as a novel target to block the transition from acute to chronic pain.

14. I became concerned with bad outcomes resulting from chronic use of opioids in the early 2000s within my own teaching hospital as I became aware of opioid-induced respiratory failure and/or lack of analgesic response in patients administered various formulations and doses of opioids. One of the most dramatic concepts was the idea, promoted at the time, that one could achieve effective analgesia for any pain problem by simply increasing the dose, strength and/or frequency of an opioid to overcome a patient’s complaint of severe pain over time. As an example, an unfortunate young woman had developed graft versus host disease following a bone marrow transplant resulting in a progressive sloughing (desquamation) of her skin (80% burn) and enteral lining leading to severe pain plus extensive GI bleeding. The administration of increasing doses and infusions of fentanyl over several weeks, despite continued complaints of 10+/10 pain, resulted in her receiving the unimaginable doses of 3.4 liters of fentanyl per day. In fact, her pain appeared to be getting worse instead of better despite the enormous doses of fentanyl (Eilers et al. 2001). Fortunately, with the addition of the analgesic adjunct low-dose ketamine, that had not previously been used in our institution for the

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potential treatment of opioid tolerance and hyperalgesia, we were able to reverse this life-threatening direction and wean off the fentanyl, achieve analgesia and discharge her from the ICU (Eilers et al. 2001).

15. This outcome seemed at odds with the idea of opioids having no ceiling effect. More broadly, I began to examine the marketing about the purported opioid efficacy and low risk of addiction with the use of long-term opioid use and OxyContin. My studying the issue, and figuring out how to deal with it, prompted me to question what had become the status quo—and not just for chronic pain, but how we were managing opioid-naïve patients entering the hospital for elective joint replacement and many leaving on long-term opioids including OxyContin. Because many in the medical community, including myself, were persuaded at the time that opioids were safe and effective for long-term use, there was less concern about providing 30 or even 60-day supplies for acute injuries / post-operative recoveries. Overall, many physicians at the time, having been persuaded that opioids were safe if used as prescribed, believed patients would use what they needed and no more, and therefore having extra was not a problem. At some level, longer discharge prescriptions also reduced the need for doctors to schedule follow-up visits for refills. As the decade progressed and I engaged in a number of educational and operational initiatives to improve the safety of opioid use in the hospital, I also engaged in programs to reduce the burden of opioids through the introduction of multimodal analgesia to reduce the prescription of opioids during and upon discharge. I was especially struck by a paper published by Dr. Susan Okie in 2010, “A Flood of Opioids, a Rising Tide of Deaths” (Okie 2010), which succinctly presented the tragic consequences of unintended overdose and death from prescription opioids.

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16. The Okie paper motivated me to do more at my institution in this area, including directing multiple “UCSF Pain Summits” and other educational efforts to trainees and physicians.

B. Understanding the Biology of Opioids and Pain

1. What is an opioid?

17. Opioids are compounds that work at opioid receptors in the central and peripheral nervous system that are involved in modulating the sensation and perception of pain. These include opiates: naturally occurring alkaloids found in opium, including morphine, codeine, thebaine, and papaverine. Opioids also include synthetic and semi-synthetic compounds often with potencies greater than morphine. Whether naturally occurring in the opium poppy or fully synthesized in a chemist’s laboratory, all of these opioids are classified as “exogenous opioids”—external to the body. There are also “endogenous opioids,” which occur within the body. The most commonly known group of endogenous opioid peptides are the endorphins. Popular culture descriptions of a “runner’s high” or “endorphin-boosting exercises” refer to the body’s own opioid system, which is critical to many bodily functions. When people take exogenous opioids—whether Vicodin (hydrocodone), morphine or heroin—they are consuming a substance that fits into the body’s own analgesic system like a progressively oiled key in a lock.

18. Depending on their intrinsic activity or efficacy, opioids may be classified as full agonist, partial agonists, and antagonists. The receptor-activating properties and affinities of opioid analgesics can be manipulated by pharmaceutical chemistry to make them more or less potent, and depending on their delivery system, longer lasting.

Opioids have numerous effects on the central nervous system, including analgesia (pain relief), euphoria, depression of the nervous and respiratory systems, cough suppression, and

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constipation. With respect to analgesia, unlike other non-opioid analgesic drugs, opioids can reduce both the sensory and affective (emotional) components of pain. Opioids relieve severe, constant pain from tissue injury, such as after trauma or a surgery but appear to be largely ineffective for intermittent shooting pain caused by nerve damage. Opioids can do a good job controlling pain when someone is not moving but a poor job blocking movement-triggered pain.

19. Many patients experience euphoria or a pleasant floating sensation with lessened anxiety and stress especially when taking an opioid for the first time. In general, the greater an opioid's potency and the faster it crosses into and acts on the central nervous system, the more likely the person will experience euphoria and a floating sensation. In the case of oxycodone, there has been growing concern that oxycodone is not merely a compound with superior bioavailability (better oral absorption than morphine), but possessed other properties that increased its abuse liability (Remillard, Kaye, and McAnally 2019). These include that unbound oxycodone concentrations in brain at steady state will be approximately six-fold higher than those of morphine due to differences in the extent of blood-brain barrier transport (oxycodone > morphine) (Bostrom, Hammarlund-Udenaes, and Simonsson 2008). In addition, the action of oxycodone has been shown to have an enhanced ability to evoke the stable increase in dopamine concentrations as well as the phasic properties of dopamine release in a critical reward site of the brain, the nucleus accumbens (Vander Weele et al. 2014). Taken together, these reports suggest that oxycodone represents an opioid analgesic with increased abuse potential.

20. Opioids act on the nervous system in many ways, but they generally act as nervous system depressants causing sedation—drowsiness and clouding of mentation. Opioids that have full activity (affinity – efficacy) at the mu opioid receptor, will dose-dependently

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decrease the breathing rate. Independent of their role in treating pain, weaker opioids are routinely used for cough suppression.

21. Some of the most medically concerning effects of opioid use in the context of chronic use are tolerance, dependence, and addiction. Tolerance refers to the problem of repeated doses of opioids having a diminishing analgesic effect. Chronic opioid users will also develop a tolerance to the other opioid effects such as respiratory depression, although this does not protect them from fatal overdose. Opioid tolerance develops at different rates to different effects. The exception to opioid tolerance is constipation; the body does not develop a tolerance to this effect. With respect to pain relief, after repeated doses, attaining the same quality of analgesia experienced with early exposure to opioids requires progressively increasing the dose and or potency of the opioid. Despite dose increases, it is rare that a patient will have the same degree of analgesia experienced during their initial dose.

22. Physical dependence accompanies tolerance to repeated administration of opioids. For example, after a period of regular opioid administration, failure to continue the drug results in withdrawal or an abstinence syndrome (an exaggerated rebound of the nervous system from having lost its suppressed state). In the context of long-term use, dependence is not only physical, but psychological, and becomes much harder to reverse.

23. Addiction is a primary, chronic disease of brain reward, motivation, memory, and associated circuitry. Dysfunction in these circuits leads to characteristic biologic, psychological, and social manifestations. Addiction is characterized by inability to abstain consistently, impairment in behavioral control, cravings, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. A

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pneumonic is the four C's: Cravings, loss of Control of amount or frequency of use, Compulsion to use, use despite Consequences.

2. What is pain?

a. Pain is a perception.

24. The International Association for the Study of Pain (IASP) defines "pain" as "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Pain is always subjective, even when it is associated with objectively observable tissue damage.

b. Chronic pain is not simply another day of acute pain.

25. Chronic pain is frequently defined as pain that lasts beyond the normal tissue healing time, and generally estimated at pain lasting 3 months or longer.

26. Chronic pain encompasses a complex condition that has defied simple remedies. Persistent pain has been classified as chronic if someone has endured it for at least three months. Unfortunately, over this time period, the person experiencing chronic pain may have changed in complex ways. A single therapeutic switch to turn off the perception of chronic pain has yet to be found and in fact may not exist. From the neuroscientist's perspective, pathologic plasticity changes in the central and peripheral nervous system have taken hold and have become self-perpetuating, signaling pain and frequently limiting meaningful function. It often is associated with negative changes in mood, driving depression and social isolation. From the perspective of those suffering chronic pain, any remedy, even one that may simply remit the pain for a few hours or days, may be a welcome relief despite risks or side effects. Importantly, just as chronic pain represents a complex pathophysiologic condition that develops over time, the successful management of chronic pain often requires an equally complex and time-intensive approach to

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diminish or resolve. While opioids can provide effective immediate pain relief, they do not reverse the pathophysiologic states of chronic pain.

3. History of Opioid Use

27. Over the past 25 years the United States has experienced an unprecedented increase in opioid-use disorder (OUD, which is sometimes used interchangeably with “addiction”), opioid overdose, and other opioid-related harms. As of 2017, 2.1 million Americans aged 12 years or older had an OUD involving prescription opioids, and about 700,000 had an OUD involving heroin, an illicit opioid (HHS 2018). Drug overdose, driven primarily by opioids, is now the leading cause of unintentional injury death in the United States. Two out of three drug overdose deaths involve an opioid (Hedegaard H 2018). Overdose deaths from opioids have increased almost six times since 1999 (CDC 2018). Overdoses involving opioids killed more than 47,000 people in 2017, and 36% of those deaths involved prescription opioids (Scholl et al. 2018). This increase in opioid-related deaths has occurred in tandem with an equally unprecedented increase in the prescribing of opioid medications for purposes of pain management.

28. This latest chapter in the modern medical use of opioids in this country represents a significant departure from the one preceding it. Below I provide a brief outline of the historical context leading up to the current situation.

a. For centuries, doctors have known that opioids are one of the most potent analgesic agents available, but they have also known that opioids are highly addictive.

29. Opioids have been used for medicinal and recreational purposes for millennia. While the use of opioids for treatment of acute severe pain has generally been accepted, their use for managing chronic noncancer pain has been controversial since the 19th century, with the popular view shifting over the decades between broad acceptance versus a more restrictive

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perspective (Courtwright 2001). The tension between the desire to make opioids available to those who may benefit from them and the recognition that opioids are addictive drugs with societal consequences was heightened with medical developments that occurred during the 1800s (Musto 1999; Booth 1996; Courtwright 2001). These developments included the extraction of morphine from opium in 1803 and the development of the hypodermic needle (which can be used to inject morphine to relieve pain) in the 1850s (Courtwright 2001). Morphine was used widely for pain management during the American Civil War, and many soldiers developed opioid addiction or “morphinism.” With few effective alternatives, moreover, many medical professionals used morphine to treat chronic pain conditions. This and the nonmedical use of opioids were major drivers of an opioid addiction epidemic that took place in the latter 19th Century (Courtwright 2015).

30. By the late 1800s, scientists were starting to recognize the problem of opioid addiction, and a policy response began to emerge. What is thought to be the first accurate and comprehensive description of addiction to morphine was produced in 1877. In hopes of developing a less addictive alternative to morphine, heroin (diacetylmorphine) was synthesized in 1874 (although it was later found to be more potent than morphine). Medical professionals became increasingly critical of the use of opioids to treat pain and lobbied successfully for state and local laws to control the sale of opioids and other narcotics. Consumption of medicinal opioids declined as a result (Courtwright 2015).

31. Reform efforts continued in the early 20th century. The Harrison Narcotics Act, enacted by Congress in 1914, required persons who imported, produced, sold, or dispensed opium-based drugs (as well as coca-based drugs) to register, pay a tax, and keep detailed records that officials could use in enforcing laws to restrict opioid transactions to legitimate medical

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channels. This act had the effect of criminalizing the use of opium for nonmedical purposes (Courtwright 2015; Hoffman 2016). The use of heroin for medicinal and other purposes was specifically banned by the Heroin Act, enacted in 1924.

32. The consensus among medical professionals for most of the 20th century was that opioids should not be used for the management of chronic pain because of the lack of evidence regarding their effectiveness for this type of pain and the risk of addiction. For example, in a survey of physicians in the early 1970s, “when asked why they would not go higher [in dosing meperidine] if pain persisted, 40% of the doctors stated that higher doses were no more effective, with 60% stated that higher dosages contained the danger of serious side effects.” (Marks and Sachar 1973) Some researchers even concluded that doctors were under-prescribing opioids due to an exaggerated fear of addiction (Morgan 1985). Research aimed at developing new and potentially less-addictive opioids continued. Nevertheless, Percocet (oxycodone) and Vicodin (hydrocodone) which combined semisynthetic opioids with acetaminophen, became available in the 1970s for relief of moderate to moderately severe pain. These and most other prescription opioids are now regulated under the Controlled Substances Act (CSA) of 1970 as Schedule II drugs—those with a “high potential for abuse which may lead to severe psychological or physical dependence” (DEA 2019).²

b. Increased opioid prescribing in 1990s for cancer and palliative care

33. The stigma associated with opioids meant that they often were not used or were used sparingly even for people with terminal cancer. American physicians worked to change this approach and expand the use of opioids for cancer and palliative care.

² Some opioids are not classified in Schedule II. These include opioids containing less than 90 milligrams of codeine per dosage unit (e.g., Tylenol with Codeine®) and buprenorphine (used in the treatment of OUD), which are Schedule III drugs—those with “a potential for abuse less than substances in Schedules I or II” and whose “abuse may lead to moderate or low physical dependence or high psychological dependence” (DEA, 2019).

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34. Globally, 8.2 million people die of advanced cancer each year. Cancer pain prevalence rises with disease progression and affects about 64% of patients with advanced cancer, and about 45% of all patients with advanced cancer experience pain of moderate to severe intensity (Patijn et al. 2007). Morphine and other strong opioids have been critical to help manage pain in advanced cancer. Historically, modern day efforts to improve pain control for patients with cancer have their roots in the mid- sixties when the first hospice was founded in England, often using opiates for treatment of end-of-life pain. However, concerns were raised in the 70s, 80s and beyond that a portion of cancer pain remained undertreated. For example, based on structured interviews, authors suggested that misconceptions about opioids probably led to undertreatment with narcotic analgesics, causing much needless suffering in medical inpatients. Upon closer examination of a case study however, the vast majority of the cases noted were pain complaints from cardiac ischemia with a single traumatic case of pain (rib fracture) and no control group or randomization (Marks and Sachar 1973). Other arguments were promoted about the undertreatment of pain (Deandrea et al. 2008; Greco et al. 2014). This included a movement in the 1980s from some cancer patients and physicians to legalize heroin for cancer pain. Given the limited study design, the relative efficacy of heroin versus morphine in the relief of chronic cancer pain remains incompletely studied (Levine, Sackett, and Bush 1986).

35. Although pain management in cancer patients differs, these variations were not explained by cancer type, duration of disease, or socioeconomic deprivation. In response to the reported disparities and undertreatment of cancer pain, there emerged initiatives to expand the scope of cancer pain care including the use of opioid analgesics (Portenoy et al. 1986; Foley 1985). The failure to use more opioids in the treatment of cancer pain was depicted as an

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irrational, undocumented fear that appropriate use will lead patients to become addicted (Morgan 1985).

36. In 1986, the World Health Organization (WHO) published a “ladder” guideline for opioid use with progressive cancer pain. Even then, however, the WHO explicitly distinguished its recommendations for cancer pain from chronic pain:

It is important to stress that a clear distinction exists between patients with chronic non-malignant pain and patients with pain from progressive cancer. Extensive clinical experience has demonstrated that, while most cancer pain responds readily to established clinical treatments, this is not true of many nonmalignant, chronic pain syndromes. Severe cancer pain commonly responds to strong opioid drugs, whereas this is not the case for most forms of non-malignant chronic pain.

(‘Cancer pain relief, World Health Organization’ 1986). Other efforts to measure the quality and quantity of cancer pain management by measuring the amount of morphine consumed in a particular country argued against the association between increases in morphine consumption and opioid addiction. However, the data actually showed that 9 of 11 European countries with an increase in morphine consumption had an increase in overdose rates from 1986-1990 (Zenz and Willweber-Strumpf 1993).

37. Subsequently, it was emphasized that effective treatment of cancer pain often required much more than increasing doses or potencies of opioids. To better address this challenge, guidelines were developed through the “National Comprehensive Cancer Network. Adult Cancer Pain” that included recommendations to reevaluate pain at each patient visit and as needed to meet patient-specific goals for comfort, function, and safety through comprehensive pain management. This includes the consideration of a pain management specialty consultation (Comprehensive and Network 2016). Thus, even when treating pain from active cancer, best practices for pain management require a comprehensive response rather than opioids alone.

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- c. **The multidisciplinary treatment of chronic pain provided a safe and effective model of care. But under pressure from market forces, the number of multidisciplinary pain centers declined in the 1980s and chronic pain treatment shifted back to primary care.**

38. As is often noted, the scientific discipline of pain research and the medical subspecialty of pain management are relatively new fields, notwithstanding the prevalence and universality of pain (Tompkins, Hobelmann, and Compton 2017). John J. Bonica, an anesthesiologist, is widely considered to be the father of modern pain management. He designed and operated the first “multidisciplinary” pain clinic at the University of Washington in Seattle in the 1960s (Tompkins, Hobelmann, and Compton 2017). The clinic brought together clinicians from a variety of fields, including physicians, psychologists, nurses, occupational therapists, physical therapists, and vocational counselors all of whom were trained in pain management. This team would meet collectively to discuss ongoing patient care issues, and the assessment and treatment options they designed were comprehensive, including “behavioral treatment for chronic pain, physical therapy, occupational therapy, and ability to refer to specialists not offered by the team” (Tompkins, Hobelmann, and Compton 2017). This approach achieved success. The following passage from a recent paper sums up the evidence supporting multidisciplinary pain treatment:

Due to improvement in overall patient functioning, reductions in health care expenditures and an increase in rate of patients returned to employment, the multidisciplinary pain clinic was deemed a success (Flor, Fydrich, and Turk 1992) (Kamper et al. 2015). In these published meta-analyses, multidisciplinary pain clinics were compared to single discipline treatment (e.g., physical therapy, medication management), usual medical care, and/or no treatment. Impressively, treatment gains remained evident for up to 13 years (Patrick, Altmaier, and Found 2004; Roberts, Sternbach, and Polich 1993). Analyses of patient outcomes revealed that it wasn’t any single component of the clinic treatment that led to improvements in pain outcomes, but rather an effect of the concerted biopsychosocial team approach ((Linssen and Spinhoven 1992; Schatman 2010) Schatman, 2010). Subsequently, the number of pain clinics and accredited pain fellowship programs flourished, most of which used opioid therapy sparingly due to concerns of addiction and poor outcomes (Meldrum 2003). These early clinics were multidisciplinary using similar methods to Bonica’s original model, or clinics focused on

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a single pain syndrome (e.g., migraine headaches) or single treatment modality (e.g., providing nerve blockade or physical therapy) (Bonica 1990).

(Tompkins, Hobelmann, and Compton 2017).

39. Yet, notwithstanding ample evidence demonstrating the effectiveness of the multidisciplinary approach (Flor, Fydrich, and Turk 1992; Turk 2002; Turk and Okifuji 1998; Guzman et al. 2001), the number of multidisciplinary pain clinics started to decline in the 1990s while the number of opioid-focused and other single modality clinics increased. This reversal has been unfortunate: multidisciplinary pain clinics that provide a form of treatment that is evidence-based and proven effective have decreased while the number of opioid-focused single modality clinics that provide a form of treatment that is neither evidence-based nor proven effective has increased. This result is even more unfortunate since one of the documented positive outcomes of the multidisciplinary approach to pain treatment was decreased use of opioids. (Turk and Okifuji 1998) (noting “[o]ne study documented that 65% of patients seen at clinics before enrolling in a pain management program used opioids compared with 20% of patients at discharge from a pain management program. Another study found that 73% of patients reduced their use of opioids while in a pain management program.”).

40. The decline in the number of multidisciplinary pain clinics has been attributed to “economic” realities or factors present in the American healthcare system, primarily relating to insurance reimbursement, managed care, and the structure of academic medical facilities, which after the introduction of managed care, emphasized high profit subspecialties over multidisciplinary pain treatment programs (Tompkins, Hobelmann, and Compton 2017) (Schatman 2010). Multidisciplinary pain clinics, while providing effective and cost-efficient relief, tended not to be profit centers and were viewed by insurance companies as more expensive than other forms of pain relief. As discussed below, Purdue and other opioid

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manufacturers encouraged the transition to opioid-focused treatment. But even in the absence of stand-alone multidisciplinary pain clinics, the approaches endorsed by such clinics remained safer and more effective treatment for chronic pain than opioid-focused treatment.

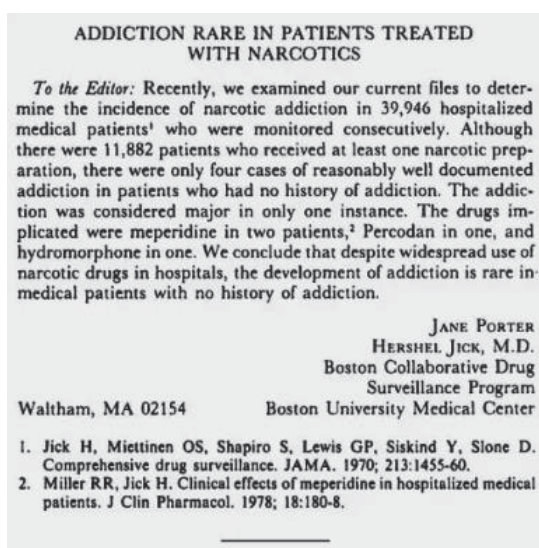
- d. In the mid-nineties, OxyContin came on the scene, and there was an enormous push by Defendants to expand the use of opioids for chronic conditions, with higher doses prescribed, longer periods of treatment and for an increasing number of conditions.**

41. Despite the country's history of opioid abuse and addiction during a time in which opioids were prescribed liberally for many conditions, a movement began to expand the use of opioids to provide pain relief for persons suffering from chronic pain. This movement had at its origin what appears to have been a genuine effort to replicate the success treating cancer pain in the chronic pain fields. There was debate during this early movement to expand the use of opioids for chronic pain among physicians advocating this approach, and those preferring a multidisciplinary approach to treating chronic pain that was showing significant evidence of effectiveness, as discussed above (Munglani 2019).

42. Against this backdrop, and the desire of the medical community to provide effective pain relief for the many Americans suffering from chronic pain, came a new opioid formulation that promised relief without the risk of addiction and abuse that so marked the history of opioids. In 1995 the FDA approved OxyContin (oxycodone controlled-release), which was manufactured by Purdue Pharma and marketed as allowing dosing every 12 instead of every 4 to 6 hours (FDA, 2017c). Purdue marketed OxyContin aggressively to providers and patients in the years following its release to the market in 1996 (Meldrum 2016). This marketing drove the prescription of OxyContin / oxycodone at higher doses, longer periods of treatment, and for an increasing number of conditions—despite evidence of high abuse potential.

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43. Purdue and other manufacturers took the message of expanding opioid use that the cancer and palliative care specialists had begun to advance and amplified it. By repeatedly citing two pieces of “evidence” and sponsoring multiple presentations on the topic, the manufacturers multiplied the reach of this message by many times more what it otherwise would have been for an academic research physician publishing papers. This was despite the fact that one of the two sources repeatedly cited was only a letter to the editor and had a very limited scope given it reviewed files of hospitalized patients who had received “at least one narcotic preparation” while in the hospital to determine the incidence of addiction (Porter and Jick 1980):



44. Manufacturers nonetheless cited this letter for the broad claim that fewer than 1% of patients treated with opioids would develop addiction, as discussed below.

45. As later reviewed by Leung et al, this single letter to the editor, leveraged by Purdue in support of OxyContin, was subsequently cited 608 times, while other letters to the editor published contemporaneously were cited a median of 11 times (Leung et al. 2017). Although the Porter & Jick letter was published in 1980, it was cited most frequently between

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1996 and 2002, with the highest frequency in 1996, the same year that Purdue began marketing OxyContin (Leung et al. 2017).

46. Nor did the other source most frequently cited provide strong evidence supporting chronic opioid use (Portenoy and Foley 1986). Portenoy and Foley sought to demonstrate that opioid maintenance therapy can be a safe, salutary and more humane alternative to the options of surgery or no treatment in those patients with intractable non-malignant pain and no history of drug abuse. However, these conclusions were built on a very limited case study that was descriptive rather than analytic, with small non-random patient selection and where two-thirds required less than 20 morphine equivalent mg/day (Portenoy and Foley 1986). At best, this study supported a conclusion that more study was needed. It did not support the conclusions that Purdue and other opioid manufacturers claimed to expand the market for prescription opioids.

47. Although there was little dispute at the time of the importance of more effectively treating cancer pain, an overwhelming emphasis on opioids appeared to take hold with the expanded use of OxyContin over more comprehensive approaches to treat pain. Purdue used the oncology market as an entrée for OxyContin, but its sales representatives then quickly moved to primary care, with the message to treat not only cancer pain but essentially all moderate to severe painful conditions with OxyContin/oxycodone, as discussed in more detail below.

48. Purdue essentially co-opted the messaging coming out of the cancer pain movement and advanced the notion that opioids were an ideal therapeutic solution, underused for the long-term management of chronic pain, and that the risks of addiction were very small. Purdue recognized, however, that if OxyContin was considered a cancer drug, doctors would be reluctant to use it more broadly. To avoid this result, Purdue scrupulously avoided comparing

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OxyContin to the opioid most associated with cancer (morphine) or stating that OxyContin was as strong as morphine (when in fact the oxycodone is stronger).

49. In 1996, the American Academy of Pain Medicine and American Pain Society issued a joint consensus statement titled *The Use of Opioids for the Treatment of Chronic Pain*, describing potential benefits of using opioids for management of chronic pain (including non-cancer) (Haddox et al. 1997). This included statements that promoted the use of opioids for chronic non-cancer pain, that the risk of prescription opioids causing addiction was a myth, and chronic pain can be measured on a 0 to 10 scale as easily as acute pain (Campbell 1996). Moreover, it was argued by this group that studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low and the risk of opioid-induced respiratory depression tends to be a short-lived phenomenon that generally occurs only in the opioid-naive patient, and is antagonized by pain (Haddox et al. 1997)—a dangerous position that was never grounded in rigorous science and has been proven wrong (Dowell, Haegerich, and Chou 2016).

50. There were also concerted efforts by pain specialists funded significantly by Purdue and the other opioid manufacturers to persuade state medical boards and state legislatures to remove legal impediments to opioid-based pain treatment (Hoffman 2016). This was accompanied by a campaign to call public and professional attention to the prevalence of pain and its seriousness as a public health problem. This concept was also supported by the American Academy of Pain Medicine and American Pain Society to advocate for the interests of pain patients suggesting that pain be considered a “5th vital sign,” ostensibly in an effort to improve pain assessment and treatment. (Campbell 1996). Although increasing attention was drawn to the assessment and treatment of pain, there was little to no progress in the development of novel pain

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therapies. The intersection of a greater societal focus on pain management and pain as an emerging 5th vital sign, without any fundamental advance in analgesics beyond more opioids, left physicians searching for solutions—a marketing opportunity capitalized upon by pharmaceutical companies emphasizing the effectiveness and safety of new extended-release opioids.

51. With the incorporation of measuring pain as the 5th vital sign, it soon became apparent that its application was not providing its intended outcome—the improvement of pain care. In a retrospective study of 300 visits before and after the institution of the 5th vital sign, Mularski and colleagues found no improvement in pain management (Mularski et al. 2006). More concerning was that, following the institution of the 5th vital sign and adoption by the Joint Commission, risk to patients increased as a result. Subsequently, new standards recommend that pain assessment include identification of psychosocial risk factors that may affect self-report of pain, promote access to nonpharmacologic pain treatment modalities, and avoid 5th vital sign algorithms that would result in opioid-based patient harm (Baker 2017).

52. In the context of Purdue’s substantial promotional expenditures and these changing professional attitudes, OxyContin sales rose from \$48 million in 1996 to more than \$1 billion by 2000 (Van Zee 2009). Sales of prescription opioids are estimated to have quadrupled between 1999 and 2010 ('Vital signs: overdoses of prescription opioid pain relievers - United States, 1999-2008' 2011), driven in part by OxyContin during the early portion of this period (GAO 2003). However, problems began to emerge by at least 2000, with reports of widespread diversion, tampering, and misuse of OxyContin (Cicero, Inciardi, and Munoz 2005) (GAO 2003; Hoffman 2016). In response, the FDA changed the OxyContin label in 2001 “to add and strengthen warnings about the drug’s potential for abuse and misuse” and in 2003 issued a

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warning letter to the manufacturer regarding promotional materials that omitted and minimized the drug's safety risks (FDA 2017).

53. Nonetheless, sales of prescription opioids continued to increase (Pan 2016). The increase in opioid prescribing that began during the 1990s was associated with a parallel increase in opioid-related substance use disorders and opioid-related deaths (Dowell, Haegerich, and Chou 2016; Kolodny et al. 2015). Using conservative estimates excluding non-methadone synthetics, prescription opioids overdoses accounted for 17,087 deaths in 2016, up from approximately 3,442 in 1999 (Seth et al. 2018). While there are indications that opioid prescribing is decreasing, as recently as 2017, tens of millions of opioids were dispensed in the U.S. (191 million total opioid prescriptions) (CDC 2017). Although recent data do show a leveling off in opioid prescribing, rates in the United States remain at historically high levels and substantially greater than the rates seen in other industrialized Western countries. These high prescribing rates continue despite the lack of evidence supporting such practices and the abundant evidence of the risks and harms of opioid use. The rates of prescription and illicit opioid misuse, a shift from prescription opioids to illicit markets, overdose, and admissions to drug treatment programs have all increased in parallel to burgeoning opioid prescribing (Rudd et al. 2016).

IV. DETAILED STATEMENT OF OPINIONS

54. This opioid crisis lies at the intersection of two substantial public health challenges: containing the rising toll of opioid-related harms and reducing the burden of suffering for the tens of millions of people suffering from pain. Finding the ideal balance is a challenge for all physicians and health care providers. While there are a number of reasons why the epidemic was able to take root in the Country—from the lack of medical education on the

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treatment of pain, to the market forces that caused a decrease in the availability of multidisciplinary pain treatment—there is no real question that the epidemic has been driven by an unwarranted increase in prescription opioids orchestrated by the pharmaceutical industry. The total opioid prescribing rate more than doubled in the U.S. from 1995 to 2013 (IMS Health 1997-2013). This trend is confirmed by prescription data from 1995-2010 derived from the National Ambulatory Medical Care Survey showing a substantial increase in opioid prescriptions between 1995 and 2010 in office-based medical visits, especially in visits by middle-aged and older adults and by patients making their first visit to the treating physician (Olfson et al. 2013).

A. The medical standard of care for treating both chronic and acute pain was changed because of widespread promotion and marketing of opioids that trivialized the risk of addiction and exaggerated the benefits of long-term opioid use.

55. As part of our work on the NASEM Consensus Study Report, my colleagues and I relied on a traditional multi-factorial causal model commonly used in public health, ranging from structural factors to individual susceptibility. Using this approach, we found certain hypotheses about “causes” of the epidemic to be inescapable. Of particular note, data present a prima facie case that heavy promotion of opioid prescribing by Defendants (including misleading claims), substantially increased prescribing by physicians and was the key contributor to the increase in misuse, OUD, and accompanying harms. (Van Zee 2009; GAO 2003; Hoffman 2016; Cicero, Inciardi, and Munoz 2005; 'Vital signs: overdoses of prescription opioid pain relievers - United States, 1999-2008' 2011).

56. Opioid manufacturers took advantage of physicians’ desire to provide relief to large population of people with chronic pain conditions. In 2016, the CDC estimated 50 million US adults suffer chronic pain, defined as reporting pain every day or most days over the past 6 months; and 19.6 million U.S. adults suffer from “high-impact chronic pain,” defined as chronic pain that frequently limits life or work activities (Dahlhamer et al. 2018). The CDC explains:

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“National estimates of high-impact chronic pain can help differentiate persons with limitations in major life domains, including work, social, recreational, and self-care activities from those who maintain normal life activities despite chronic pain, providing a better understanding of the population in need of pain services.” (Dahlhamer et al. 2018) Chronic pain, however, is complex and difficult to treat.

57. While multidisciplinary pain treatment demonstrates substantial effectiveness, for the reasons discussed above, access to this type of treatment diminished in the 1990s. Yet, of course, physicians’ desire to help their patients remained. It is, thus, particularly unfortunate from a public health perspective that it was at this precise moment that Purdue’s unprecedented marketing campaign for OxyContin took shape (GAO 2003). It was fertile ground for a campaign based on the promise that these opioids were new and improved and specifically designed to provide effective relief for chronic pain with very low risk of addiction.

1. The campaign to persuade doctors to prescribe “new” opioids

58. In my opinion, the driving force of this national catastrophe has been the introduction and marketing of long-acting formulations of high potency opioids such as OxyContin beginning in 1996. Physicians were misled through Defendants’ marketing and sales detailing intended to persuade doctors to accept that more potent and long-acting formulations of opioids (such as OxyContin) were safe and effective in the treatment of multiple forms of pain, especially chronic non-cancer pain, and even at high doses.

59. Purdue and other Defendants utilized a number of approaches to encourage physicians to prescribe opioids broadly for the treatment of chronic pain. They engaged in direct-to-consumer marketing. They marketed directly to physicians through sales representatives. They funded research, pain-related medical societies, and continuing medical education, lobbied medical boards and agencies responsible for pain-related treatment guidelines,

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and lobbied state and local government to remove barriers to broader use of opioids for the treatment of pain. ('Fueling an epidemic. Exposing the financial ties between opioid manufacturers and third party advocacy groups' 2018). A common feature across all of these efforts to promote the broader use of opioids was the message that the risk of addiction was rare, and the benefits of long-term opioid use were well established. These efforts were remarkably successful:

An in-depth analysis of the promotion and marketing of OxyContin (Purdue Pharma, Stamford, CT), a sustained-release oxycodone preparation, illustrates some of the key issues. ... OxyContin's commercial success did not depend on the merits of the drug compared with other available opioid preparations. The *Medical Letter on Drugs and Therapeutics* concluded in 2001 that oxycodone offered no advantage over appropriate doses of other potent opioids. Randomized double-blind studies comparing OxyContin given every 12 hours with immediate-release oxycodone given 4 times daily showed comparable efficacy and safety for use with chronic back pain and cancer-related pain. ... In 2001 alone, the company spent \$200 million in an array of approaches to market and promote OxyContin.

From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences... Purdue promoted among primary care physicians a more liberal use of opioids, particularly sustained-release opioids. ...

Purdue's promotion of OxyContin for the treatment of non-cancer-related pain contributed to a nearly tenfold increase in OxyContin prescriptions for this type of pain, from about 670 000 in 1997 to about 6.2 million in 2002... Prospective, randomized, controlled trials lasting at least 4 weeks that evaluated the use of opioids for chronic, non-cancer-related pain showed no consistent improvement in physical functioning. ...

When OxyContin entered the market in 1996, the FDA approved its original label, which stated that iatrogenic addiction was "very rare" if opioids were legitimately used in the management of pain. In July 2001, to reflect the available scientific evidence, the label was modified to state that data were not available for establishing the true incidence of addiction in chronic-pain patients [and] also deleted the original statement that the delayed absorption of OxyContin was believed to reduce the abuse liability of the drug.

...Purdue funded more than 20 000 pain-related educational programs through direct sponsorship or financial grants, providing a venue that had enormous influence on physicians' prescribing throughout the country.

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(Van Zee 2009). Evidence I have reviewed, including Defendants' internal communications, sales representative training materials and call notes, and promotional materials supports Dr. Van Zee's conclusions. A number of examples of this information are attached to my report as Exhibits A-C. These examples are not intended to be exhaustive, but, rather, illustrative of the Defendants' actions.

60. It is my opinion that as a result of direct-to-consumer and direct-to-physician marketing, as well as other efforts by opioid manufacturers to promote the widespread and long-term use of opioids, that the risk of addiction was trivialized, and the benefits of long-term opioid use overstated. Physicians were influenced by these efforts and a cautious and conservative approach to the use of opioids for the treatment of pain was replaced with much more liberal prescribing practices. I observed this firsthand in my own training after emerging from residency in 1995 to find increasing use of more potent formulations of opioids and sustained-release opioids for acute and chronic noncancer pain.

2. Specific misstatements designed to encourage physicians to overcome their reluctance to prescribe opioids liberally for chronic pain

61. Opioid manufacturers promoted chronic use of opioids based upon a set of key misrepresentations. These included the following: (1) taking long-acting opioids as prescribed for pain protects against addiction and abuse; (2) that new opioid formulations had no ceiling dose and were safe at high doses; and that (3) chronic opioid therapy improves function and quality of life. These misrepresentations appeared in print promotional materials and were also repeated by sales representatives in their direct marketing to physicians. In addition, (4) Purdue, at OxyContin's launch, took advantage of and was careful to maintain the perception that oxycodone is less potent than morphine, when in fact it is more potent.

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a. Opioid manufacturers claimed taking long-acting opioids as prescribed for pain protects against addiction and abuse.

62. As discussed above, in 1996 when OxyContin was released, physicians generally were reluctant to prescribe opioids on a long-term basis because of fears of addiction. Purdue, of course, knew this through market studies that demonstrated this concern. Purdue admitted this when it pled guilty in 2007 to misbranding OxyContin:

During the period February through March 1995, PURDUE supervisors and employees obtained market research that included focus groups of forty primary care physicians, rheumatologists, and surgeons to determine their receptivity to using OxyContin for non-cancer pain. According to this market research, some of these physicians had concerns, similar to their concerns about combination opioids, regarding OxyContin's addictive potential and side effect profile, including that “[t]he biggest negative of [OxyContin] was the abuse potential.”

See Agreed Statement of Facts, *United States. v. Purdue Frederick Co.*, No. 1:07-cr-00029 (W.D. Va. May 10, 2007) (“Purdue Guilty Plea”) at §19. Internal documents produced in discovery confirm Purdue’s knowledge of physicians’ reluctance to prescribe opioids for non-cancer pain. See Exhibit C. For example, notes from a June 9-11, 1995 OxyContin Investigators’ Meeting indicate that “among health care providers there is a perception that patients feel a ‘stigma’ associated with opioid analgesic therapy. Morphine and hydromorphone are most associated with this stigma. One of the patients’ biggest fears appears to be the possibility of addiction...” PKY181823986 at 17 (See Exhibit C-2).

63. Sales representatives used multiple approaches to persuade physicians who expressed caution and concerns about the abuse and addiction potential of oxycodone and OxyContin. See Exhibit A. This amounted to repeated falsehoods that OxyContin / oxycodone had a decreased potential for addiction, was superior to and a less addictive alternate than combination forms of opioid analgesics containing hydrocodone (equal potency to morphine)

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and acetaminophen. One of the ways Purdue overcame this reluctance was by persuading doctors that OxyContin was a “new” formulation of oxycodone that was less likely to be abused or lead to addiction. *See* Exhibit A-1.1, Exhibit B-1-15. OxyContin is simply oxycodone (which was developed in 1917) in a timed-release formulation that Purdue argued allowed a single dose to last 12 hours, mitigating the potential for addiction. Specifically, Purdue said, the extended-release mechanism maintained drug levels at constant levels. *See* Exhibit A-3.1-3.6. This marketing explanation for why this pill could be used with little risk of addiction, while plausible (because highs and lows (or “peaks and troughs”) were understood to be tied to the development of addiction) lacked scientific proof. At no point was this marketing claim—or the use of opioids for chronic pain generally—supported by reliable evidence of the type that should have accompanied widespread marketing of the drug. Indeed, Purdue eventually admitted that its statements claiming that its extended release formulation made OxyContin less addictive than immediate release formulations was false and misleading (*see* Purdue Guilty Plea).

64. Moreover, Purdue knew from its own pharmacokinetic studies that OxyContin’s peaks and troughs were not significantly different from those of IR oxycodone, but Purdue concealed that data. Purdue admitted this deception in the Purdue Guilty Plea at §§21-27. In fact, for many patients, OxyContin only lasted for 8-hours, after which patients would experience a decline in analgesic effect (or trough). Purdue worked to prevent physicians from prescribing OxyContin Q8 (or every 8 hours) despite its knowledge that this end-of-dose drop-off was common. *See* Exhibit A-3 For example, an exhibit that refers to “Q12h vs. Q8h Warfare,” indicates that sales representatives were told, “the action of adding a dose, as opposed to increasing the Q12h dose, needs to be nipped in the bud. NOW!!.” They were further advised that “the war is on – OxyContin is a true 12h product. Help the MD see that 12h is appropriate

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dosing for the patient controlling the pain, enhancing quality of life, even if it means using an escalating dosage and number tablets.” PPLP003996830 (*See* Exhibit A-3.6).

65. It is evident from Purdue salesperson call notes that Purdue heavily marketed this purported steady state, 12/hr efficacy of OxyContin and purportedly lower abuse potential. *See* Exhibit B. For example, a September 20, 1999 call note from Ohio states:

SAYS USES OXY, MOSTLY FOR NURSING HOME PATS. HE SAID HE HEARD IT NOW HAD A LOWER BACK PAIN INDICATION -- TOLD HIM STUDIES HAVE BEEN DONE FOR BACK PAIN, OSTEOARTHRITIS, AND CANCER -- DISCUSSED NO CEILING, 12HR EFFICACY, BLOOD LEVELS, LOWER ABUSE POTENTIAL. DISCUSSED FAST FOR NURSING HOME PATS.

Exhibit B-7, PPLPMDL0080000001 (excel spreadsheet, row 129292). Another call note from Ohio dated November 7, 1997 states:

ALWAYS RELUCTANT TO USE NARCS BUT TOLD IF GOING TO PUT PT ON VIC/LORT OR TYL 3, WHY NOT USE THE 12 HR DOSED, WITHOUT TYLENOL AND LESS ABUSE POTENTIAL.

Exhibit B-4, PPLPMDL0080000001 (excel spreadsheet, row 76265). And another from November 19, 1997 from West Virginia states:

CONCERNED ABOUT ADDICTION WITH OPIOIDS. DIFFERENCE BETWEEN DEPENDENCE AND ADDICTION. LESS THAN 1% OF PATIENTS BECOME ADDICTED. CAN ABRUPTLY STOP LOW DOSES OF OXYCONTIN WITHOUT WITHDRAWAL SYMPTOMS.”

Exhibit B-8, SHC-000008118.

66. Promotional information given to doctors and print advertising promoted the same false messages about 12/hr dosing, low abuse potential or risk of addiction resulting from chronic opioid use. *See* Exhibit A. In addition to misleading physicians about 12/hr dosing, Purdue and the other opioid manufacturers pushed the notion more generally that the risk of addiction was rare when prescription opioids were used “as prescribed.” Thus, it was not just that 12/hr dosing, round-the-clock treatment was safer and more effective, but also that addiction was unlikely to occur—indeed it would rarely occur so long as the patients taking the pills were

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in pain and were following doctors' orders. Again, this shows up in promotional materials and call notes, not only from Purdue, often citing studies that purportedly proved these points. There are many examples of this in the materials I reviewed. Some particularly troubling instances include the following:

- “In fact, the rate of addiction amongst pain patients who are treated by doctors is much less than 1%.” --- Transcript of “I Got My Life Back” Purdue promotional video, featuring Dr. Alan Spanos (2000) PKY180989588 at 10 (Exhibit A-1.12).
- “Fact: Fears about psychological dependence are exaggerated when treating appropriate pain patients with opioids.” --- Purdue Professional Sales Aid – Myths about Opioids (2001) PURCHI-000674082 at 11 (Exhibit A-1.13).
- “Addiction risk also appears to be low when opioids are dosed properly for chronic, noncancer pain.” --- Purdue Professional Sales Aid – Myths about Opioids (2001) PURCHI-000674082 at 11 (Exhibit A-1.14).
- “Pain relief is an important medical reason to take opioids as prescribed by your doctor. Addicts take opioids for other reasons, such as unbearable emotional problems. Taking opioids as prescribed for pain relief is not addiction.” --- Endo brochure, Understanding Your Pain: Taking Oral Opioid Analgesics (2004) ENDO-CHI_LIT-00084049 at 3 (Exhibit A-1.16).
- Endo, *Taking a Long-Acting Opioid: What does it mean to me?* (2008) ENDO-CHI_LIT-00024520 (Exhibit A-3.14):

**What is the risk of becoming addicted
to a long-acting opioid?**

Addiction is defined as compulsive drug seeking that is beyond a person's voluntary control even if it may cause harm. Most healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.

- Mallinckrodt, Exalgo Learning System (training for sales representatives): MNK-T1_0001161164 at 29 (*See* Exhibit A1.19-) (“While most patients chronically taking opioids for medical reasons develop tolerance and physical dependence, the risk of addiction is low.”).

67. Overall, sales representative detailed the recurrent message that Oxycontin represented the next line in analgesic choice after NSAIDS, was superior to hydrocodone, and

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had less abuse potential. Sales representatives frequently quoted the Porter and Jick letter for the claim that fewer than 1 % patients develop addiction when taking opioids for chronic pain. But there is in fact no medical evidence supporting this and other statements about the low risk of addiction, and it was misleading to suggest that the Porter and Jick letter, or the Portenoy and Foley 1986 study of 38 patients on low-dose opioids, supported these broad statements.

b. Opioid manufacturers misleadingly represented that new opioid formulations had no ceiling dose and were safe at high doses.

68. “New” ER opioids were promoted as safe at high doses unlike older low-potency combination drugs with acetaminophen. In addition, doctors were told that there were no ceiling doses for Oxycontin or other long-acting opioids.

69. There are, again, many examples of marketing and promotion materials in which doctors and patients are told that the dose can be increased safely (titrated up) until the pain is “under control.” For example, a Purdue 2003 OxyContin conversion guide provided the following information, indicating no dose limit and the message to “Continue titrating by 25% to 50%, if necessary”:



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See PDD1501128421 at 35 (Exhibit -A-3.16).

70. Similarly, a 2004 brochure from Endo Pharmaceuticals, *Understanding Your*

Pain: Taking Oral Opioid Analgesics explains:

IF I TAKE THE OPIOID NOW, WILL IT WORK LATER WHEN I REALLY
NEED IT?

Some patients with chronic pain worry about this, but it is not a problem.
The dose can be increased or other medicines can be added.
You won't 'run out' of pain relief.

ENDO-CHI_LIT-00084049 at 4 (Exhibit A-1.16).

71. Call notes also show that sales representatives pitched the notion of no dose limits and safety at high doses. *See* Ex. B. For example, a Purdue sales representative noted in a July 6, 2000 note from Ohio:

“SPOKE WITH MD WHO EXPRESSED CONCERN RE: ONE PT
RECEIVING 120 MG Q 12 FOR BACK PAIN-DISCUSSED THE PFACT
THAT THERE IS NO CEILING DOSE WITH OXY LIKE SHORT ACTING;
HE SEEMED TO THINK THAT THIS PT WAS ABUSING THE PRODUCT;
HE NEEDS REAFFIRMATION RE: THE DECREASED ABILITY OF OXY
TO BE ABUSED AND DECREASING NUMBER OF TABS....”

PPLPMDL0080000001, Exhibit B-12. Similarly, a January 19, 2001 call note from a Purdue sales representative in Ohio notes: “doc said he has been using oxy for awhile and that he uses high doses, i reminded doc there is no ceiling and that he should not worry about how high he needs to go.”). PLPMDL0080000001, Exhibit B-14.

72. A particularly troubling feature of this is testimony that drug representatives received higher compensation for selling higher dose opioids.³

³ *See* Exhibit A-2.1, Excerpt of Deposition of Karen White, a sales representative for Purdue from 1998 to 2002, 98:23-99:14, Dec. 17, 2003, PKY182895039 (“[i]t would exponentially affect our bonuses. I mean if we got the doctor, as I mentioned earlier, to write an 80 milligram instead of a 10 milligram, we would make seven and a half times more money based on what percentage of our sales that we increased over our quota.”); *see also* Sposato Dep. 18:21-19:2, PDD9520404001. (“Q. My question is: Same amount of pills, higher dosage, Purdue makes more money for the higher dosage, correct? A. That’s correct. Q. And that factors into someone’s bonus, correct? A. Possibly.”); ENDO-OPIOID_MDL-04908071 at 4 (2002 Endo “Tsunami Launch IC Plan” incentivized the Endo

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73. The daily clinical consequences of the myth of no-ceiling dose is reflected in the increasing number of opioid-dependent patients. What was once unimaginable is now common: to see a patient taking over 500, or even 1,000 MMEs (oral morphine equivalents) daily admitted to our hospital and continue to complain of severe pain. It is a myth that there is no ceiling dose with opioids as illustrated by very real risk and consequences of overdose and death from long-term opioid therapy. Mortality rates increased gradually across the range of average daily milligrams of morphine equivalents indicating a single threshold of harm does not exist. Thus, there are no single inflection points defining a threshold of opioid risk/safety. The situation becomes even more dire if benzodiazepines are taken concurrently. The higher the dose, the higher the risk of death; this risk may occur for some patients at doses that previously were thought to be “safe.” (Dasgupta et al. 2016).

74. Other studies have also examined the relationship between long-term opioids and overdose and death. Persons who received 3 or more opioid prescriptions within 90 days for chronic noncancer pain between 1997 and 2005 and received 50 to 99 mg/d of opioids (compared with 1 to 20 mg/d) had a 3.7-fold increase in overdose risk, while patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (Dunn et al. 2010). Higher opioid doses were associated with increased risk of opioid overdose death with a maximum prescribed dose of 100 mg/d or more (Bohnert et al. 2011). When the risk of overdose was examined in patients taking a daily dose of less than 20 mg versus those with average daily doses of 200 mg or more of morphine (or equivalent), there was a nearly 3-fold increase in the risk of opioid-related mortality (Gomes et al. 2011). Other patient cohorts have shown even greater risks at a

sales force to meet the goal of “pushing higher doses” with “rewards that increased steeply” for “deeper penetration into the high-strength [Oxy/APAP] market”—defined as Percocet 7.5/325 and 10/325 and all Oxy/APAP 7.5/500 and 10/650 variants (Percocet, Endocet, and Generic Oxycodone/APAP).

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threshold of intermediate dosing (>40 morphine milligram equivalents) with an odds ratio of 12.2 (CI 9.2-16.0) (Paulozzi et al. 2012).

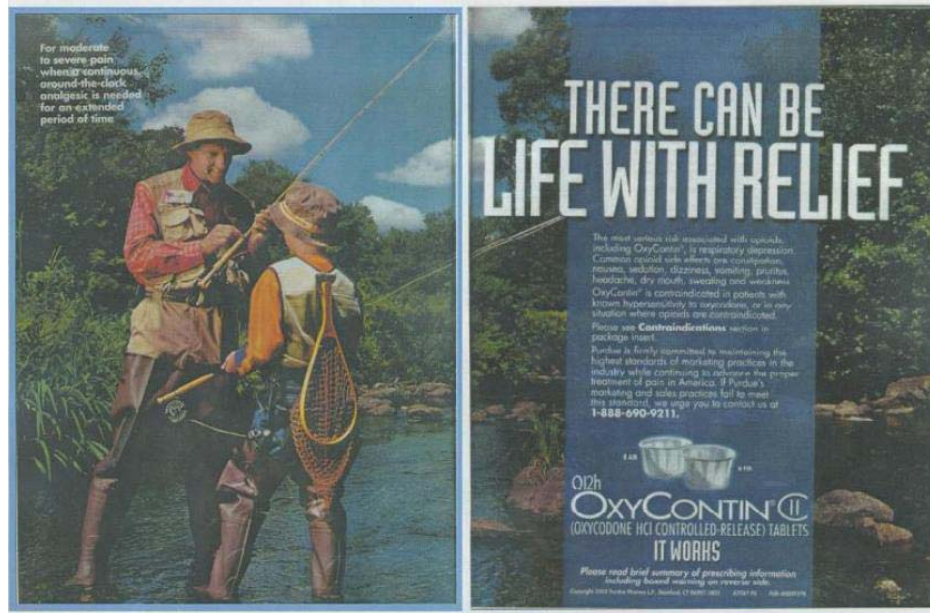
75. Taken together, with more recent studies, it appears that there is no minimum threshold below which risk of harm is zero, and risk generally increases with daily dosing. The notion that taking less than 100 MME / day is somehow safe is not supported by the literature and represents a sobering conclusion that the unnecessary initiation of long-term opioid therapy has the potential of causing great harm at any dose (Zedler et al. 2014; Bohnert et al. 2016).

c. Opioid manufacturers misleadingly represented that chronic opioid therapy improves function and quality of life.

76. Opioids were marketed for years as the panacea for pain that would give patients back their lives. The now notorious 1998 Purdue promotional video featuring Dr. Spanos, “I got my life back,” painted a picture of a miracle drug at work. See PKY180989588 (Exhibit A-1.12). Patient brochures and advertisements similarly told people that opioids could improve their health, function and quality of life. Some examples include:

- “Myth: Opioids make it harder to function normally. Fact: When used correctly for appropriate conditions, opioids may make it easier for people to live normally.” --- Janssen patient guide, *Finding Relief: Pain Management for Older Adults* (2008) JAN-MS-00476773 at 10 (Exhibit A-1.21).
- “Multiple clinical studies have shown that long-acting opioids, in particular, are effective in improving: Daily function, Psychological health, Overall health-related quality of life for people with chronic pain.” --- American Pain Foundation, *A Policymaker’s Guide to Understanding Pain & Its Management* at 29 (2011) (See Exhibit A-1.22).
- Purdue 2006 ad for OxyContin, “There can be life with relief”: PDD1501614879 at 3 (Exhibit A-1.23).

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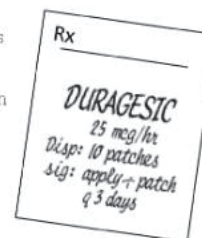


- JAN-MS-00306286 at 8 (Exhibit A-1.24).



Give your patients the freedom of a life
uninterrupted by chronic pain

- Uninterrupted pain relief for up to 72 hours with fewer peaks and troughs
- Helps patients think less about their pain
- Improvements in physical and social functioning



Duragesic®
FENTANYL TRANSDERMAL
SYSTEM

Life, uninterrupted.

77. The impression created by these materials is that opioids are safe and effective, seldom harmful, and usually beneficial. But opioids—whether formulated as immediate-release or extended-release, and with or without “abuse-deterrent features”—are dangerous and highly

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addictive. But that certainly was not the message communicated by Purdue and the other manufacturers. Instead, doctors and patients were told that studies proved that opioids would improve function and enhance quality of life for persons suffering from chronic pain. There was no scientific basis for these statements when made, and abundant evidence developed over time showing that long-term opioid therapy, rather than improving function and quality of life, leads to poor functional outcomes.

78. For example, in a Danish health study, opioid usage was significantly associated with reporting of moderate/severe or very severe pain, poor self-rated health, not being engaged in employment, higher use of the health care system, and a negative influence on quality of life. Put otherwise, opioid treatment of long-term/chronic non-cancer pain does not seem to fulfill any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity (Eriksen et al. 2006). In fact, the odds of recovery from chronic pain were almost 4 times higher among individuals not using opioids compared with individuals using opioids (Sjogren et al. 2010). There is also evidence that return to work is more often delayed than expedited for patients on chronic opioids (Von Korff 2013; Franklin et al. 2008; Franklin et al. 2009).

d. Purdue promoted and encouraged confusion about the strength of oxycodone.

79. Physicians were reluctant to prescribe opioids, particularly morphine, because of the stigma. Morphine was a cancer drug, and it was known to be highly addictive. Purdue worked around this problem by taking advantage of confusion about the active ingredient in OxyContin. Purdue knew that physicians often believed oxycodone was less powerful than morphine - when in fact, it was stronger. As explained by Purdue's former CEO Michael Friedman in an email to Richard Sackler on April 22, 1997:

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Oxycodone has a ‘personality’ that is influenced by many years of oxycodone use in Percocet. We have built a large part of our platform on this personality and used it to differentiate OxyContin from MS Contin and This differentiation has lead [sic] to much non-malignant business. Marketing is not only about what you are. It is also about what you are not. We have a success beyond our expectations that is, in part, due to the unique personality of OxyContin.

PPLP004030162 at p. 1 (Exhibit C-9). Purdue admitted that it was “well aware of the incorrect view held by many physicians that oxycodone was weaker than morphine” and “did not want to do anything ‘to make physicians think that oxycodone was stronger or equal to morphine.’”

Purdue Guilty Plea at ¶29. Similarly, and as noted above, Purdue was careful not to describe OxyContin in any way that suggested that it was as strong as morphine – when in fact, it was stronger. Examples of this are provided in Exhibit C, including:

- Email from M. Cullen, June 2, 1997, PPLP004032323 at p. 4 (Exhibit C-6) (“Since the non-cancer pain market is much greater than the cancer pain market, it is important that we allow this product to be positioned where it currently is in the physician's mind. If we stress the “Power of OxyContin” versus morphine, it may help us in the smaller cancer pain market, but hurt us in the larger potential non-cancer pain market. Some physicians may start positioning this product where morphine is used, and wait until pain is severe before using it.... It is important that we not change the position perception of physicians towards oxycodone when developing promotional pieces, symposia, review articles, etc..”).
- Friedman Email to R. Sackler, May 28, 1997, PPLP004030150 at 1 (Exhibit C-5 at 5) (“it would be extremely dangerous, at this stage in the life of this product, to tamper with this ‘personality,’ to make physicians think the drug is stronger or equal to morphine.”).

80. Doctors were reluctant to prescribe morphine for chronic pain because they understood the risk of abuse and addiction. By perpetuating confusion regarding the strength of oxycodone, and the purportedly less-addictive attributes of the extended-release mechanism, Purdue changed prescribing practices.

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B. Opioid manufacturers took advantage of their ability to influence physicians through direct-to-physician marketing, medical education, and industry-sponsored and -funded KOLs.

81. Opioid manufacturers took advantage of physicians' desire to provide relief to the large population of people with chronic pain conditions. Chronic pain is complex and difficult to treat. While multidisciplinary pain treatment demonstrative substantial effectiveness, for the reasons discussed above, access to this type of treatment diminished in the 1990s. Yet, of course, physicians' desire to help their patients remained. It is, thus, particularly unfortunate from a public health perspective that it was at this precise moment that Purdue's unprecedented marketing campaign for OxyContin took shape. It was fertile ground for a campaign based on the promise that this opioid was new and improved and specifically designed to provide effective relief for chronic pain with very low risk of addiction.

82. Studies show that detailing is effective.⁴ In addition, KOLs and mentors play a significant role educating physicians. They are highly influential, they are trusted – when a department head, or well-known and prominent academic physician says this is how you treat this condition, doctors follow suit. Residency is hierarchical; residents are students who learn from their seniors, like an apprenticeship. And when presented with studies supporting the view of the KOLs – that is influential, too.

83. Although it is unknown precisely the depth of the influence opioid-related industries such as Purdue may have had on academics, published literature and their influence on

⁴ See e.g., Datta A and Dave D. Effects of Physician-directed Pharmaceutical Promotion on Prescription Behaviors: Longitudinal Evidence. *Health Economics*. April 2017;26(4):450-469; Stros M and Lee N. Marketing dimensions in the prescription pharmaceutical industry: a systematic literature review. *J of Strategic Marketing* 2015;23(4):318-336; Anon. Persuading the Prescribers: Pharmaceutical Marketing and its Influence on Physicians and Patients. November 11, 2013. <http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients> Accessed August 13, 2018; Gonul, F., Carter, F., Petrova, E., & Srinivasan, K. (2001). Promotion of prescription drugs and its impact on physicians' choice behavior. *Journal of Marketing*, 65, 79–90.

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faculty as Key Opinion Leaders, the failure to disclose industry-academic relationships is insidious and has undoubtedly impacted the practice of a generation of providers and trainees (Fauber 2011a). When confronted with conflict of interest, some academic centers have curtailed their relationships with these industries (Fauber 2011b).

84. These and other forces were brought to bear on providers both in private practice and academics and I believe exerted a strong influence. As a result, the standard of care was changed across the country. Compounding the problem was the limits of medical education on how to treat pain generally, and especially chronic pain. There is no common pain management curriculum that is broadly utilized for US medical, dental, pharmacy, or nursing schools that would be of similar rigor as, for example, the evaluation and treatment of chest pain. As of 2010, a survey of 117 US and Canadian medical schools concluded that pain curriculum was limited in time and scope (Mezei and Murinson 2011).

85. Although the majority of medical schools contain some pain curriculum, it is primarily embedded in other core course structures and is not generally regarded as a stand-alone topic. Alternately, much of pain management has been taught on the wards from senior to junior trainees. In 2010, the National Institutes of Health (NIH) Pain Consortium held a workshop on the state of pain education in the United States—overall there was inadequate education and training in pain management across the country. Opioid manufacturers took advantage of this education vacuum. Through the message that doctors could provide chronic pain relief to their patients, with simply the administration of OxyContin every 12 hours, and with very effective messengers—both drug representatives and prominent medical leaders in the field of pain management—the standard of care for treating pain was changed.⁵

⁵ The fact that detailing is proven to be highly effective means that it has the potential to influence provider practice, and it has also been shown to be effective prescriber education outside of the sales context, with what is referred to

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C. For the vast majority of chronic pain patients, the risks of prescription opioids significantly outweigh any benefits, and that at most, a small percentage of chronic pain patients achieve meaningful relief from the long-term use of opioids

86. At most, opioids are properly indicated for the short-term treatment of severe acute pain (e.g. trauma or post-surgical pain); end-of-life pain/hospice care; and cancer pain from active malignant disease. Chronic opioid therapy is not recommended for most common chronic pain conditions, including low back pain, centralized pain such as fibromyalgia, and headache pain. In less common chronic pain conditions (such as pain from advanced multiple sclerosis, sickle cell disease, pain following spinal cord injury and paraplegia, or post-herpetic neuralgia), which comprise a small percentage of chronic pain patients, opioids may be considered a third-line therapy (taken if other therapies are ineffective or contraindicated) for moderate and severe pain. However, in other neurologic conditions such as polyneuropathy, no functional status markers were improved by long-term use of opioids, adverse outcomes were more common among patients with polyneuropathy receiving long-term opioids, including depression opioid dependence and opioid overdose (Hoffman et al. 2017).

87. In addition to diagnosis, clinicians should consider risk, and some patients may not be suitable candidates on the basis of that risk.

88. Given the narrow categories that may indicate opioids for chronic use, opioids' position as third-line therapy, and the significant risks associated with its use, long-term opioid therapy for persons with chronic pain conditions is, at most, indicated in fewer than 5% of patients with chronic pain and likely significantly fewer, as explained below.

as "academic detailing" or sometimes "systems consultation." See Avorn J, Soumerai SB. Improving drug therapy decisions through educational outreach. A randomized controlled trial of academically based "detailing." N Engl J Med 1983; 308:1457-1463. As providers search for professional guidance in applying emerging evidence to their opioid prescribing practices, such educational detailing from trusted colleagues will be critical to separate fact from fiction among the pervasive marketing environment that surrounds the current practice of medicine in the United States.

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89. For all proper indications other than terminal cancer, palliative care and hospice care, if prescribed, opioids should be prescribed with the lowest effective dose of immediate-release opioids taken only when needed.

1. Opioids are not recommended for most common chronic pain conditions.

90. The use of opioids for the management of chronic pain represents the rationale for the prescribing of a large percentage of overall opioid medication consumed each year in the United States. Common types of pain for which these drugs are prescribed include back pain, arthritis, and neuropathic pain (e.g., pain involving tissue injury). Yet there is only minimal evidence of effectiveness of opioids for successful management of chronic pain from rigorous studies lasting more than 6 weeks (Chou et al. 2015). Amongst the complications now associated with the chronic use of opioids for pain are withdrawal, dependence, tolerance, hyperalgesia, diversion, misuse, abuse, addiction, hypogonadism (specifically low testosterone in men, and amenorrhea/dysmenorrhea in women), falls, fractures, sleep-disordered breathing, increased pain after surgery, and poorer surgical outcomes, immunosuppression, and increases in feeding and growth hormone that can lead to weight gain. (Baldini, Von Korff, and Lin 2012; Chou et al. 2015).

91. In the case of the most common chronic pain conditions, including low back pain, centralized pain such as fibromyalgia, and headache pain, patients have better outcomes if opioid treatment is avoided. These conditions together comprise the vast majority of chronic pain complaints, with low back pain being the most commonly reported chronic pain condition. (Henschke, Kamper, and Maher 2015; Breivik et al. 2006; Gran 2003; Freburger et al. 2009).

92. Several meta-analyses examine the efficacy of opioids in specific pain conditions such as neuropathic (Gaskell et al. 2016; McNicol, Midbari, and Eisenberg 2013) and back pain (Abdel Shaheed et al. 2016; Chaparro et al. 2014). Additional analyses have included

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publications reporting studies involving participants with mixed types of chronic pain (Chou et al. 2014; Pedersen et al. 2014). In general, these meta-analyses have suggested that any positive effects have been demonstrated only for relatively short terms, and that the size of the effects observed were small. Long term (>1yr) outcomes are largely lacking. Dropout in opioid studies for chronic pain due to side effects is common as is discontinuation of therapy in clinical settings making it difficult to estimate the benefits of these drugs. Essentially no widely-accepted guidelines suggest that opioids should be used as first-line analgesic therapy for a chronic pain condition.

93. Back pain is one of the top reasons people visit a primary care or family practice physician and also predominates in other clinical domains, such in the care of veterans. Opioid treatment for low back pain shows no advantage over non-opioid medication management but does significantly increase the person's risk of harm and death. The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. There are no placebo-randomized controlled trials ("RCTs") supporting the effectiveness and safety of long-term opioid therapy for treatment of chronic low back pain (Chaparro et al. 2013), and the clinical benefits of shorter-term opioid therapy appear relatively small in comparison to the many well-documented adverse effects (Deyo, Von Korff, and Duhrkoop 2015). Nevertheless, opioids continue to be used widely in the attempt to manage back pain. Additional more recent analyses also find little evidence of meaningful pain relief provided by opioids for low back pain (Abdel Shaheed et al. 2016; Qaseem et al. 2017).

94. Recently, a pragmatic, 12-month, randomized trial with masked outcome assessments was completed in Veterans Affairs primary care clinics. Pain intensity was

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significantly better in the nonopioid group over 12 months. Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Adverse medication-related symptoms were significantly more common in the opioid group over 12 months. Results did not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain (Krebs et al. 2018).

95. Opioids are also not recommended treatment for fibromyalgia and other centralized pain syndromes (Sluka and Clauw 2016; Clauw 2015). In a review of available treatments for the chronic pain of fibromyalgia, no evidence was found from clinical trials that opioids are effective for the treatment of fibromyalgia pain (Goldenberg et al. 2016). In fact, observational studies reported that patients with fibromyalgia receiving opioids had poorer outcomes than patients receiving non-opioids and current guidelines recommend against the use of opioids for the treatment of fibromyalgia pain.

96. Headache is another common painful complaint that is unresponsive to long-term opioid therapy (Saper and Lake 2008).

2. There is only weak evidence of benefit from chronic opioid therapy.

97. Opioid manufacturers made repeated claims that the routine use of opioids for the treatment of pain, especially chronic noncancer pain, is safe and effective. However, an examination of the studies purported to support this claim fail to provide sufficient evidence. As described below, a majority of the trials were not conducted for sufficient time, patients were highly selected, excluding by design subjects with risk for misuse and/or the trial design was by “enriched enrollment” (only including people known to benefit from the study drug), and the trials used opioid doses that are low to moderate.

98. For example, a trial intended to demonstrate pain relief in a chronic condition such as chronic lower back pain sponsored by Purdue was conducted for only five days, and in

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addition, 19% of the study patients discontinued their medication before completion of the study (15 on codeine and five on acetaminophen plus codeine) (Hale et al. 1997).

99. In another study intended to support the claim that long-term repeated doses of opioids are effective and have low abuse potential, study patients were randomized to an open label, repeated-dose comparison of an anti-inflammatory drug and two opioid regimens in 36 patients with back pain (Jamison et al. 1998). However, patients continued to report moderate pain levels while taking opioids and had no change in their activity level. Although the study was under-powered to measure such an outcome, a statement was made that opioid therapy for chronic back pain was used “without significant risk of abuse.” Curiously they noted that the study drug seemed to benefit mood as much as pain and “only one participant showed signs of abuse behavior.” (Jamison et al. 1998).

100. In a randomized to double-blind treatment with placebo (n = 45) or 10 mg (n = 44) or 20 mg (n = 44) of controlled-release oxycodone every 12 hours for 14 days, one hundred six patients enrolled in an open-label trial intended to test “around-the-clock,” controlled-release oxycodone therapy for osteoarthritis-related pain (Roth et al. 2000). However, patients with as little as one month of arthritis pain were enrolled representing chronic pain patients, and 70 patients (52.6%) discontinued study participation prematurely. Interference of pain on walking ability, general activity, normal work, and relations did not reach statistical significance. (Roth et al. 2000).

101. The treatment of neuropathic pain (PHN) in a double-blind placebo-controlled study (MONTAS) evaluated the efficacy and effectiveness of oral morphine administration using defined inclusion criteria over two weeks (Maier et al. 2002). However, trial subjects were highly enriched as only 49 of 997 patients screened fulfilled the inclusion criteria for MONTAS.

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In addition, the study further defined short-term responders and other non-responders with mean pain intensity in all patients reduced by morphine from 7.8 to 5.2 (NNT: 2.2) and in 17 (35.4%) of responders from 7.4 to 2.9.

102. Other studies sought to demonstrate the longer-term efficacy of opioids in both neuropathic and musculoskeletal pain conditions, yet due to the high drop-out rate only 44% of 388 patients on open label treatments were still on opioids after therapy for between 7 and 24 months (Kalso et al. 2004). Another study, sponsored by Purdue suffered similar challenges with test subject drop out, and in this study, ambiguous adverse event reporting descriptions. For example, $67/227 = 29.9\%$ experienced a serious adverse effect with 13 possible test subjects with drug abuse behaviors, yet investigators reported 6 cases (2.6%) of possible drug misuse but no evidence of de novo addiction was observed. Importantly, seven persons died (Portenoy et al. 2007). Also, 133 subjects dropped out, so the denominator of 227 subjects, based on subjects who took at least one dose, is suspect, and the rate of drug abuse goes up as the numerator of cases stays the same while the denominator of subjects is decreased.

103. An enriched enrollment randomized withdrawal (EERW) design excludes potential participants who are nonresponders or who cannot tolerate the experimental drug before random assignment. Although EERW trial designs appear not to bias the results of efficacy, they underestimate the adverse effects (Furlan et al. 2011). Therefore studies to demonstrate opioids' efficacy in the treatment of chronic non-cancer pain for up to 3 months in such enriched trial schemes underestimate their adverse effects—a critical feature in the determination of the safety and efficacy of long-term opioids (Meske et al. 2018). Furthermore, efficacy in a 12-week study is an insufficient basis to extrapolate to long-term pain relief (Busse et al. 2018).

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104. In a 2008 review of the evidence on efficacy, Ballantyne and Shin noted the inappropriateness of relying on randomized controlled trials (RCTs) as evidence for long-term opioid therapy, remarking that “one must ask if the randomized trial really is the best form of evidence for assessing opioid treatment of chronic pain given the artificiality of the trial setting, the tendency of trials to select ‘ideal’ patients, and the lack of generalizability to the wider population that is being treated outside trials.” (Ballantyne and Shin 2008). Although RCTs are generally considered the gold standard of clinical evidence, the authors explain that “[i]n the end, RCTs tend to be useful only for showing efficacy for certain pain conditions, only for the length of the trial which tends to be short (up to 8 mo), and only in terms of the metrics of the trials.” This is problematic in the context of long-term opioid therapy given that “[a]nalgesic efficacy, as demonstrated in randomized trials, does not necessarily predict effectiveness in terms of the larger real-life goal of providing helpful pain relief that is not compromised by adverse drug effects.” The limitations of drawing on only short-term RCT studies has been noted by others, and included lack of effectiveness studies on long-term benefits and harms of opioids (Chou et al. 2009). It was also noted that chronic use of prescription opioids for noncancer chronic pain is much higher and growing faster in patients with mental health and SUDs than in those without these diagnoses (Edlund et al. 2010).

3. There is strong evidence that the risks of harms from opioid use increase with dose and duration of treatment.

105. Opioid manufacturers had no basis for representing that chronic opioid use was safe and effective. On the contrary, as evidence in this case shows, Defendants knew that the risks of harm were high and the evidence of benefit questionable. These companies nonetheless continued marketing, even as growing evidence of risk accumulated, and in fact compounded the

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problem by casting doubt on the studies demonstrating increased risk, thereby creating more confusion and prolonging sales.

106. However, the risks associated with the use of prescription opioids are numerous and can be life-threatening. What factors have driven this? In the Washington State workers' compensation system, the total number of opioid prescriptions tripled between 1996 and 2002. However, prescriptions for the most potent opioids such as oxycodone (Schedule II), as a percentage of all scheduled opioid prescriptions (II, III, and IV), increased from 19.3% in 1996 to 37.2% in 2002. Among long-acting opioids, the average daily morphine equivalent dose increased by 50%, to 132 mg/day (Franklin et al. 2005). Franklin et al. found that as injured Washington workers were given more prescriptions of higher doses of opioids, the rates of opioid overdoses among that population jumped, from zero in 1996 to more than twenty in 2005. And in 2009, over thirty people receiving opioid prescriptions through the Workers' Compensation Program died of an opioid overdose.

107. Doctors wrote 72.4 opioid prescriptions per 100 persons in 2006. This rate increased 4.1% annually from 2006 to 2008 and 1.1% annually from 2008 to 2012. It then decreased reaching a rate of 66.5 per 100 persons in 2016. A record number of drug overdose deaths occurred in 2015: 52,404. While a death may involve more than one drug, prescription or illicit opioids were involved in 63.1% of these deaths. There was a steady increase in mortality rates for natural or semi-synthetic opioids (e.g., hydrocodone, oxycodone) from 1999 to 2010, but now has been replaced by climbing rates of heroin and especially synthetics such as fentanyl. For OD deaths involving synthetic opioids other than methadone, the rate increased from 0.3 per 100,000 in 1999 to 3.1 in 2015 ($p < 0.05$) – a ten-fold increase (Annual Surveillance Report of

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Drug-Related Risks and Outcomes. Centers for Disease Control and Prevention.

<https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf>, 2017).

108. Risks of dependence and addiction are greater when opioid analgesics are used long-term than when they are used short-term (Boscarino et al. 2011). Moreover, it has been shown that once patients have been on opioids longer than 90 days, the risk that they will continue on opioids chronically and for developing a substance use disorder increase (Krashin, Murinova, and Sullivan 2016). In addition to substance use disorder (Han et al. 2017), morbidity related to opioid therapy for chronic pain includes reduced testosterone, cardiac abnormalities, fractures, and immunosuppression, among other adverse outcomes (Chou et al. 2015).

109. When randomized trials and observational studies involving adults with chronic pain who were prescribed long-term opioid therapy (opioid therapy evaluated long-term (>1 year) were examined, there was insufficient evidence to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. However, an opioid dose-dependent risk for serious harms was found (Chou et al. 2015). In other patient populations (veterans) associations have also been established between occasional and chronic opioid use and increased risk of hospital readmission, and risk of death (Mosher et al. 2014). A retrospective population-based cohort study conducted of opioid prescriptions given to patients with polyneuropathy, long-term opioid therapy did not improve functional status but rather was associated with a higher risk of subsequent opioid dependency and overdose. (Hoffman et al. 2017).

110. In a national sample of 1,424 people across Australia experiencing pain for a median of 10 years, greater daily OME (oral morphine equivalent) consumption was associated with higher odds of multiple physical and mental health issues, aberrant opioid use, problems associated with opioid medication and opioid dependence. Past-year dependence was

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independently associated with being younger, exhibiting more aberrant behaviors and having a history of benzodiazepine dependence (Campbell et al. 2015).

111. A 2015 systematic review estimated the prevalence of opioid misuse (i.e., use of opioids in ways other than prescribed despite adverse effects) in the United States to be 21.7-29.3 percent and the prevalence of addiction or continued use despite harm to be 7.8-11.7 percent (Vowles et al. 2015). In the elderly and other patients with higher risk of cognitive impairment, opioids may result in further impairment in cognition and executive function (Schiltenswolf et al. 2014). As noted earlier, there is a risk of overdose from these drugs due to opioid-induced respiratory depression (Chou et al. 2015).

112. Of the many long-term consequences of opioid use, tolerance and opioid-induced hyperalgesia (OIH) are commonly cited as reasons for waning therapeutic effect over time. Laboratory evidence is very clear that these phenomena occur after even short periods of exposure to opioids or after exposure to large doses of opioids (Angst and Clark 2006; Trang et al. 2015; Yi and Pryzbylowski 2015). Likewise, tolerance and OIH have been demonstrated in opioid addicts, and abnormal pain sensitivity in addicts is associated with drug craving (Ren et al. 2009). On the other hand, OIH has been shown after the short-term exposure to potent, rapidly eliminated opioids such as remifentanil in human volunteers (Angst and Clark 2006; Eisenach, Tong, and Curry 2015). Correspondingly, patients for whom remifentanil is incorporated into their surgical anesthetic seem to have higher postoperative pain levels or opioid requirements consistent with either tolerance or OIH (Fletcher and Martinez 2014; de Hoogd et al. 2016).

113. In sum: In the mid-1990s, there was nothing more than weak evidence of benefit from chronic opioid therapy. Opioids have not been shown to be effective for most common

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chronic pain conditions. Instead, there is strong evidence of harms, particularly with higher doses—which are exactly the doses Defendants promoted.

4. The 2016 CDC Guideline is based on a systematic review of the evidence and highlights the misleading nature of Defendants’ opioid marketing.

114. While there are many published guidelines regarding the prescription of opioids, the Centers for Disease Control and Prevention (CDC) guidelines for prescribing opioids for chronic pain are some of the most carefully constructed and influential. (Dowell, Haegerich, and Chou 2016)

115. The strength of the CDC guidelines is based on several factors including the broad range of stakeholders included in the effort, the systematic and transparent review process that was used, the inclusion of consideration of public comments, and the well-developed patient and prescriber materials that accompanied the issuance of the guidelines. In general, these guidelines urge a more conservative use of opioids. Specific conclusions tending to limit opioid use include the optimization of nonopioid therapy before a trial of opioids, the use of relatively low doses of opioids, and the recommendation to carefully follow treatment outcome and taper or discontinue opioid prescribing if the goals of therapy are not met. Further to limit dose escalation are the recommendations for the use of short-acting formulations generally having smaller dosage unit sizes and the progressive enhancement in monitoring and frequency of reevaluation has been suggested as overall doses increase.

116. The medical community recognizes the 2016 CDC Guideline as a broad standard in opioid prescribing for chronic non-cancer. It is a reasonable standard and based on a systematic review of all existing evidence. However, it is ultimately a guideline—voluntary recommendations rather than mandatory standards. The 2016 Guideline was explicitly formulated in response to the public health crisis caused by widespread prescription opioid use,

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and it is intended to discourage unnecessary and excessive opioid prescribing. Based on the evidence review conducted, the CDC Guideline states, “evidence is insufficient to determine the effectiveness of long-term opioids therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms.” The CDC’s review was informed by an earlier systematic review of the evidence on long-term opioid therapy for chronic pain (Chou et al. 2014). The Guideline strongly discourages high-dose opioid use, discourages the initiation of long-acting opioids, and strongly recommends limiting the duration of prescriptions for acute pain.

117. Since the CDC Guidelines do not establish mandatory rules as to dose and duration of therapy, they should be interpreted in a manner that does not impose sudden reduction or cessation of therapy that could be counterproductive both as to the potential for withdrawal symptoms and the possibility of patients seeking illicit opioids as an alternative. Vulnerable ‘legacy patients’ who have been on opioids for extended periods should be offered individualized therapy that provides for tapering consistent with the knowledge that the opioids themselves do not provide long-term efficacy in most patients, and that studies show improved pain status after tapering.

118. Notwithstanding the difficulties in implementation and the limitations of available evidence, it is my opinion that the CDC Guideline is a reasonable standard and one that incorporated input from the public (Lin et al. 2017) and is being widely applied in the medical community. The recommendations of the CDC Guideline for Prescribing Opioids for Chronic Pain are similar to those of opioid prescribing guidelines of other countries ('The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain' 2017; 'Opioids for persistent pain: summary of guidance on good practice from the British Pain Society' 2012; 'Quick Clinical

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Guideline for the use of Opioids in Non-Malignant Pain' 2010). These guidelines share a common goal: to improve the quality and safety in prescribing opioids for pain management and especially chronic non-cancer pain.

D. Even for those indications for which opioids are effective such as trauma or post-operative pain, the risks of prescribing opioids are significant such that non-opioid alternatives or multimodal analgesia should be used whenever possible to reduce opioid use.

1. Surgery and Acute Pain

119. Opioids are used very commonly during and following surgery. During a surgical procedure, opioids contribute to the analgesic component of a balanced anesthetic. Often the opioids used are of high potency and short duration of action to facilitate early awake times and discharge. In addition to intravenous administration, opioids are sometimes administered intrathecally or into the epidural space to provide relatively restricted analgesic effect without exposing respiratory centers in the brainstem from systemic levels of the drugs.

120. Postoperatively opioids are used in the post-anesthesia care unit, hospital wards, and as predominantly oral medications for a period ranging from days to a month or more during the convalescent period. It remains unclear how intraoperative exposure to opioids contributes to the risk for OUD. Peri-surgical exposure to opioids may be an inciting event for the eventual development of an OUD in some patients (Sun et al. 2016). Patients with OUD (e.g., individuals on methadone maintenance) are not necessarily excluded from getting a short course of opioids for acute or acute post-operative pain. More attention has been focused—appropriately, in my opinion—on reducing opioid prescribing on discharge. Providing excessive amounts of opioids postoperatively is now discouraged, and some healthcare organizations have attempted to limit the amount of postsurgical take home opioid medication.

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121. Although it is recognized that opioids have an integral role in the current practice of medicine, efforts are also underway to determine which surgical procedures and subsequent recovery can be safely achieved in the absence of opioids. For example, Summa Health System in Akron, Ohio, has drastically reduced the use of opioids in surgeries at all of its hospitals as a direct result of the opioid crisis—from using opioids in 98% of procedures in 2017 to 20% currently, with a goal of reducing that figure further to 10% or less by end of 2019. Summa Health is employing regional blocks or continuous peripheral nerve blocks in addition to a multimodal analgesia approach.⁶

122. Multimodal analgesia should be used whenever possible, including acetaminophen, NSAIDs, and non-pharmacologic therapies, to minimize opioid use. It is better to avoid opioids if there are effective alternatives. Use the lowest possible dose for the least amount of time during recovery, although higher doses and use as a first option are justified early on after injury or surgery. It is important to limit prescribing to what is actually needed, to avoid inappropriate usage, or more drug in people's medicine cabinets. After most routine surgery 3-7 days is often enough.

123. This recommendation is supported by various guidelines and sources in the medical literature, including studies demonstrating that even less than 3-7 days' worth provides adequate analgesia following many routine procedures. For example, recent literature shows that even in post-surgery settings, opioids may be unnecessary, depending on the type of surgery, as in the case of thyroid and parathyroid surgery (Shindo et al. 2018). Another study reported significant reductions in post-surgery opioid prescriptions after a new protocol was introduced: Following laparoscopic cholecystectomy, the median prescription size was 250 mg (OME),

⁶ <https://www.news5cleveland.com/news/local-news/akron-canton-news/summa-health-eliminating-opioids-from-surgeries>

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while median patient use was only 30 mg. This is equivalent to receiving 50 tablets of hydrocodone/acetaminophen, 5/325 mg, and using only 6 tablets. Evidence-based prescribing guidelines reduced prescription size by 63% without increasing the need for medication refills, thereby eliminating the excessive prescription of roughly 7000 pills. Patients also reported using fewer opioids after guideline implementation. (Howard et al. 2018). Other centers are working successfully to better define and reduce opioid dosing requirements following various surgery (Hill et al. 2017; Scully et al. 2018; Hill et al. 2018). For example, the overall amount of opioids prescribed to patients after gynecologic and abdominal surgery were reduced at the time of discharge and for the entire perioperative time for opioid-naïve patients without changes in pain scores, complications, or medication refill requests (Mark et al. 2018).

124. A growing challenge is the intraoperative and post-operative management of opioid-tolerant trauma and/or surgery patients. The fraction of patients chronically consuming opioids scheduled for surgery is approximately 20% (Mudumbai et al. 2016). This fraction may be even larger in the context of spine or orthopedic surgery where pain from the underlying diseases is frequently treated with opioids before operations are considered. Chronic preoperative opioid use whether medically sanctioned or abuse-related portends many difficulties. These include elevated levels of postoperative pain, high and unpredictable postoperative opioid requirements, and elevated risks of postoperative respiratory depression (Rapp, Ready, and Nessly 1995; Chan et al. 2017). Beyond these immediate risks, a quickly growing body of evidence suggests chronic opioid users experience poorer surgical outcomes than their opioid-free counterparts. Examples include limited restoration of function after joint replacement surgery, poorer quality of recovery after spine surgeries, and higher levels of persistent pain after gynecological procedures (Armaghani et al. 2014; VanDenKerkhof et al. 2012; Zywił et al.

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2011). More broadly, the anesthetic technique and other aspects of perioperative management used may influence the likelihood of developing postoperative pain (Richebe, Julien, and Brulotte 2015).

125. Estimating opioid dosing for opioid tolerant patients is often trial and error, but typically, if usual opioid dosages are ineffective, results in a graded / step-wise 30-50% increase in dose. As opposed to prior practice, current practice is to first exhaust other modalities of pain control, use of multimodal strategies, clonidine, ketamine, nerve blocks etc. However, these alternatives may not be available long term, and/or the patient may be unable to tolerate their introduction.

126. Another commonly encountered acute pain situation leading to opioid exposure is the treatment of acute injuries such as after household, sporting, or motor vehicle accidents. In these situations, limited supplies of opioids may be prescribed by emergency rooms, urgent care clinics, specialty physicians, and primary care providers. Emergency room opioid prescribing has been especially closely studied, and was observed to increase over the same time period that overall opioid prescribing increased (Maughan et al. 2015). Such prescribing can set the stage for a pattern of more chronic use. For example, the use of prescription opioids by former professional athletes is very high. In fact, interscholastic sports participants may have an elevated risk of opioid use and misuse compared to non-athletes (Veliz et al. 2015). Opioid prescribing for ED patients treated for ankle sprains are common. Although unusual in this population, prescriptions greater than 225 MME were found to be associated with higher rates of prolonged opioid use but could still fall within 5- or 7-day supply limit that is promoted for safer opioid prescribing (Delgado et al. 2018). Nevertheless, Emergency Departments and their respective

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associations have developed additional opioid guidelines, in line with the CDC guidelines, for the assessment and treatment of acute and acute on chronic pain in the emergency department.⁷

127. Likewise, motor vehicle accidents, particularly severe ones, appear to lead to chronic opioid use in some patients (Zwisler et al. 2015). Opioid prescribing guidelines targeting emergency rooms and other acute care settings may to a degree reduce opioid prescribing and increase the use of measures such as urine drug screening prior to prescribing (Chen et al. 2016; del Portal et al. 2016).

128. A number of non-opioid pharmacologic treatments can be used to manage pain. There is evidence that in some circumstances, some non-opioids (e.g., NSAIDs) can be as or more effective than opioids at relieving pain. While each non-opioid alternative has its own indications and risks, some are likely to be just as if not more effective than opioids for reducing pain associated with the conditions for which they are indicated and, when used appropriately, carry lower risk of adverse outcomes.

129. Even though opioids may be effective for some people in certain situations involving acute pain, it is not true that opioids are always the most effective treatment for acute pain. For example, opioids are actually less effective for control of dynamic pain that occurs with movement. According to the Oxford Pain Group League table of analgesic efficiency for acute pain, cyclooxygenase (COX) inhibitors such as diclofenac and celecoxib have a lower “number needed to treat” (NNT)⁸ than opioids in these circumstances.

⁷ <https://www.aaem.org/UserFiles/file/Emergency-Department-Opioid-Prescribing-Guidelines.pdf>

⁸ NNT or “number needed to treat” is a statistical concept that offers a measurement of the impact of a medicine or therapy by estimating the number of patients that need to be treated in order to have an impact on one person.

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2. Dentistry

130. It has been estimated that dentists prescribe 12 percent of all the immediate-release opioids (hydrocodone, oxycodone), behind only family physicians (Denisco et al. 2011), although rates may have declined in recent years (Levy et al. 2015). It is my opinion that, as with prescribing opioids for acute pain and perioperative pain generally, opioid prescribing in dentistry increased as a result of the broader change in the standard of care and overall perception of low risk from opioid treatment, which allowed dentists to feel comfortable sending patients home with longer prescriptions than what would be predicted as necessary for pain relief.

131. Dentists prescribe opioids mainly for a short term to treat acute postsurgical pain. Third molar extraction, for example, is probably the most common surgical procedure performed in healthy adults. It is estimated that 3.5 million third molar extractions are operated by oral and maxillofacial surgery specialists per year (this number does not include the exactions performed by general dentists). Ibuprofen was indicated as the peripherally acting postsurgical drug of choice by 73.5 percent of the oral surgeons in one study, however, 85 percent of them almost always prescribed a centrally acting opioid alone or in combination with another analgesic agent. Hydrocodone is among the most commonly prescribed opioid by oral surgeons, with one study showing that this was usually with acetaminophen and 20 tablets are prescribed on average (Moore et al. 2006). Based on this data at least 3.5 million people with an average age of 20 years (average age for third molars extraction) may be exposed to opioids related to dental treatment (Denisco et al. 2011). Importantly, a recent study showed that a substantial proportion of adolescents and young adults are exposed to opioids through dental clinicians and these dental

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prescriptions may be associated with an increased risk of subsequent opioid use and abuse (Schroeder et al. 2019).

132. Opioids also may be prescribed for dental pain in emergency departments (EDs). ED visits for a non-traumatic dental condition are concluded in 45 percent of the cases with an opioid prescription (Okunseri et al. 2014). It is important to note that non-traumatic acute dental pain can be treated with relatively simple dental procedure in the dental office. However, most EDs are not equipped, staffed, or designed to provide dental care.

133. Leftover opioids prescribed by dentists may be a concern if they are shared with friends or family members to help with apparent symptoms of pain, or for other reasons (O'Neil and Hannah 2010). Mandatory checking of prescription drug monitoring program data was shown to be effective in changing the prescription pattern for pain medications by dentists in a dental urgent care clinic in New York State (Rasubala et al. 2015). Therefore, it is recommended that opioids be prescribed only for several days following the oral surgical procedure. Although there is a paucity of literature regarding the duration of pain following oral surgery, 2-3 days' treatment is often thought to be sufficient (Biron et al. 1996). Moreover, extended severe pain after oral surgery may indicate infection or other complication and a visit to the dentist is better option than prolonged treatment with opioids or other painkillers. In addition, treatment with peripherally acting analgesic agents, such as ibuprofen and naproxen, has been shown to provide good pain relief (Moore et al. 2015) that can be as effective as opioids for many patients who undergo impacted tooth extraction (Hersh et al. 1993). Non-opioid analgesic agents such as NSAIDs may be considered the first line of therapy for the routine management of acute postoperative dental-related pains for patients who do not have contraindications to its use (Becker 2010; Donaldson and Goodchild 2010).

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134. Another concern is the influence that long-term opioid users may have on opioid naïve family members. Adolescent and young adult family members of long-term opioid users had an increased risk of persistent opioid use after a subsequent surgical or dental procedure (Harbaugh et al. 2019).

3. Cancer-Related Pain and End-of-Life Care

135. The aggressive use of opioids has long been accepted and strongly promoted for the treatment of pain in patients with cancer or who are in end-of-life and palliative care. Foundational work in this area suggested that control of pain due to active cancers could be achieved using oral analgesics including opioids in most patients. Such data led to the construction of the World Health Organization “Analgesic Ladder” discussed above, which outlines the use of progressively stronger analgesics as necessary to control pain (WHO, 1986). The pain, palliative care, and oncology literatures are replete with studies of various short- and long-acting opioids used to control cancer pain, generally with positive results. It was within the contexts of cancer and palliative care that the concept of “breakthrough” pain treatment gained popularity. This in turn has supported the development of fast-acting high-potency opioid preparations such as trans-mucosal and intranasal products. Overall, the aggressive use of opioids for control of pain in cancer and palliative care patients is common and strongly supported by available literature and by the medical community (Hadley et al. 2013) (Schmidt-Hansen et al. 2015) (Wiffen, Wee, and Moore 2016) (Zeppetella and Davies 2013).

136. However, the use of opioids in these populations is not without caveats. For example, nausea, constipation, sedation, and other side effects are common after the administration of opioids in cancer pain patients just as they are in those suffering from other pain conditions. Accidental overdose can occur and patients with cancer diagnoses are subject to

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increased risk of opioid mortality in a dose-response relationship, with a hazard ratio (HR) of approximately 6 at doses between 50-100 mg/day MME, and HR of approximately 12 at doses > 100 mg/day MME. Therefore, caution should be exercised in prescribing opioids to cancer patients, especially as more patients are surviving longer (Bohnert et al. 2011). Studies examining the results of urine drug screens from cancer and palliative pain patients have provided significant evidence of opioid diversion and misuse (Barclay, Owens, and Blackhall 2014; Childers, King, and Arnold 2015), while many cancer pain and palliative care clinics do not have formal policies surrounding drug misuse and diversion (Tan, Barclay, and Blackhall 2015). In addition, improperly stored or monitored medications prescribed to cancer or palliative care patients may make their way into the community.

137. An additional problem becoming more commonly recognized relates to the problem of chronic pain in cancer survivors. In addition to common non-cancer related causes, chronic pain in cancer survivors can result from the sequelae of the disease itself or treatments such as surgery, radiation, and chemotherapy. Opioids use in cancer survivors is common (Carmona-Bayonas et al. 2017). Very little data are available to quantify the frequency of opioid misuse amongst cancer survivors, but guidelines have been issued suggesting that providers use approaches similar to those employed for non-cancer patients when making decisions regarding ongoing opioid prescribing (Kurita and Sjogren 2015; Paice et al. 2016).

138. In sum, opioid use is appropriate for cancer pain from active malignant disease, as well as end-of-life pain and hospice care (defined as 6 months or less of life expectancy if disease runs normal course); however, even in these indications, opioid use is associated with risks and harm and should be balanced with a comprehensive analgesic care plan that, when appropriate, utilizes multimodal approaches.

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V. CONCLUSION

139. Chronic pain affects millions of Americans and is associated with a number of co-morbidities. While there is a pressing need to help these individuals manage their pain, long-term use of opioids has not been shown to be an effective or safe option for the treatment of chronic pain. Moreover, opioid use is associated with a number of harms, including addiction and overdose

140. The last several decades have made abundantly clear that opioids are not the answer for the vast majority of chronic pain patients. Opioids have long been used successfully for the management of acute pain (e.g., acute post-surgical and post-procedural pain), but available evidence does not support the long-term use of opioids for chronic pain management. Emphasis was appropriately placed on the need to recognize and treat of pain; however, these concerns often were not balanced with a similar emphasis on precautions to avoid adverse effects, such as development of addiction (Kolodny et al. 2015), including opioid-use disorder, opioid overdose, fractures, myocardial infarction, and others (Chou et al. 2015; Krashin, Murinova, and Sullivan 2016). Therefore, physicians increasingly prescribed opioids for chronic non-cancer pain, sometimes in very high doses, under the incorrect belief—promoted at every turn by Purdue and others—that risk for the development of substance use disorders and addiction was low (Krashin, Murinova, and Sullivan 2016).

141. Over the past decades millions of Americans have been exposed to, and many are now maintained chronically on, opioid pain medications. Many such patients have transitioned into illicit opioid markets with devastating results. Therefore, the short- and longer-term risks of opioid use are more serious than previously estimated, and the likely benefits of chronic opioid use for pain are lower for many patients than previously believed. As a result, a large group of

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“legacy” chronic pain patients continue to receive opioids at doses or under circumstances that are inappropriate in light of current knowledge.

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